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ABSTRACT

This paper examines whether physical activity influences immune function as a consequence risk of infection from the common cold and other upper respiratory tract infections (URTI) and whether the immune system responds differently to moderate versus intense physical exertion. Research indicates that people who participate in regular moderate exercise report fewer colds than their sedentary peers. Fitness enthusiasts are often uncertain of whether they should exercise or rest during sickness. Human studies are lacking to provide definitive answers, but animal studies generally support the finding that one or two periods of exhaustive exercise following exposure to viruses or bacteria lead to more frequent appearances of infection and more severe symptoms. With athletes, it is well established that sickness reduces the ability to compete. A common perception among endurance athletes and coaches is that overtraining lowers resistance to URTI. Immune function changes dramatically after each bout of prolonged, intensive exercise. Attempts to compare resting immune function in athletes and nonathletes have failed to provide evidence that athletic endeavor is linked to clinically important changes in immunity, despite compelling epidemiological data. Based on current knowledge, good immune function can be maintained by regular physical activity, eating a balanced diet, minimizing stress, avoiding chronic fatigue, and obtaining adequate sleep. (Contains 35 references.) (SM)

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# Research Digest
# Does Exercise Alter Immune Function and Respiratory Infections?

President's Council on Physical Fitness and Sports

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President's Council on Physical Fitness and Sports

Research Digest

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# Does Exercise Alter Immune Function and Respiratory Infections?

## Introduction

From birth, we are exposed to a continuous onslaught of bacteria, viruses, and other disease-causing organisms. Without an effective shield, each of us would soon succumb to infectious disease and cancer. In the battle with microbial invaders, we protect ourselves with a complex array of defensive measures collectively identified as the immune system.

The immune system is a remarkably adaptive defense entity. It is able to generate an enormous variety of cells and molecules capable of recognizing and eliminating a limitless variety of foreign invaders. There are two functional divisions: innate immunity, which refers to the basic resistance to disease that we are born with, acting as a first line of defense; and acquired immunity which, when activated, produces a specific reaction and immunological memory to each infectious agent (Mackinnon, 1999).

- *The innate immune system* includes anatomic and physiologic barriers (skin, mucous membranes, body temperature, low pH, and special chemical mediators such as complement and interferon), specialized cells (natural killer cells, and phagocytes including neutrophils, monocytes, and macrophages which can engulf, kill, and digest whole microorganisms), and inflammatory barriers. When the innate immune system fails to effectively combat an invading pathogen, the body mounts an acquired (specific) immune response.
- *The acquired immune system* includes special cells called B- and T-lymphocytes that are capable of secreting a large variety of specialized chemicals (antibodies and cytokines) to regulate the immune response. T-lymphocytes can also engage in direct cell-on-cell warfare.

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Does physical activity influence immune function and as a consequence risk of infection from the common cold and other upper respiratory tract infections (URTI)? Does the immune system respond differently to moderate compared to intense physical exertion? These important questions will be explored in this article, with physical activity and lifestyle guidelines provided to support augmentation of one's immunity and a lower risk of the common cold.

## Moderate Physical Activity and Immune Function

People who exercise regularly report fewer colds than their sedentary peers. Numerous surveys of fitness enthusiasts, runners, and masters athletes indicate that between 60% and 90% feel that they experience fewer colds than their sedentary peers (Nieman, 2000b; Shephard et al., 1995).

Data from three randomized studies support the viewpoint that near-daily physical activity reduces the number of days with sickness (Nieman et al., 1990b;1993;1998c). In these studies, women in the exercise groups walked briskly 35-45 minutes, five days a week, for 12-15 weeks during the

winter/spring or fall, while the control groups remained physically inactive. Fitness enthusiasts reported results in the same direction—walkers experienced about half the days with cold symptoms of the sedentary controls. (See Figure 1). A recent one-year epidemiological study of 547 adults demonstrated a 23% reduction in risk of upper respiratory tract infection (URTI) in those engaging in regular versus irregular moderate-to-vigorous physical activity (Matthews et al., 2000). In healthy elderly subjects, URTI symptomatology during a one-year period was inversely related to energy expended during moderate physical activity (Kostka et al., 2000).

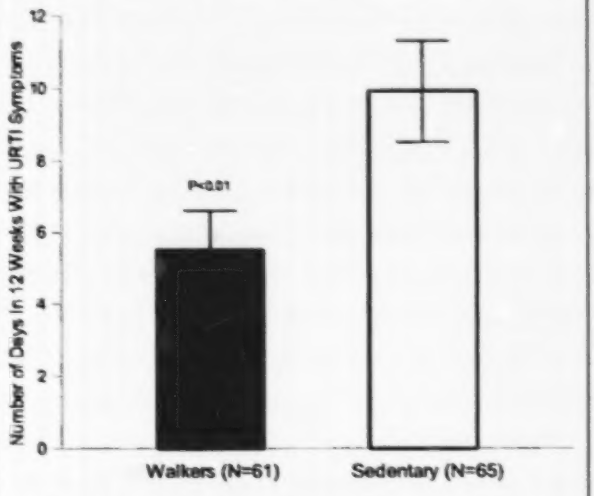


Figure 1.

Near-daily brisk walking for 45 minutes per session is associated with significantly fewer days with URTI symptoms. This figure combines the results from two studies of 126 overweight women randomized to walking and non-walking groups. Data from Nieman et al., 1990b, 1998c.

Other research has shown that during moderate exercise, several positive changes occur in the immune system (Nehlsen-Cannarella, et al., 1991; Nieman & Nehlsen-Cannarella, 1994; Nieman et al., 1999, 2000a). Stress hormones, which can suppress immunity, and pro- and anti-inflammatory cytokines, indicative of intense metabolic activity, are not elevated during moderate exercise. Although the immune system returns to pre-exercise levels very quickly after the exercise session is over, each session represents an augmentation in immune surveillance that appears to reduce the risk of infection over the long term.

Although public health recommendations must be considered tentative, the data on the relationship between moderate exercise, enhanced immunity, and lowered risk of sickness are consistent with guidelines urging the general public to engage in near-daily brisk walking.

## Rest or exercise when sick?

Fitness enthusiasts are often uncertain of whether they should exercise or rest during sickness. Human studies are lacking to provide definitive answers. Animal studies, however, generally support the finding that one or two periods of exhaustive exercise following injection of the animal with certain types of viruses or bacteria lead to a more frequent appearance of infection and more severe symptoms (Davis et al., 1997; Gross et al., 1998).

With athletes, it is well established that the ability to compete is reduced during sickness (Friman and Ilback, 1998). Also, several case histories have shown that sudden and unexplained downturns in athletic performance can sometimes be traced to a recent bout of sickness. In some athletes, exercising when sick can lead to a severely debilitating state known as "post-viral fatigue syndrome" (Maffulli et al., 1993; Parker et al., 1996). The symptoms can persist for several months, and include weakness, inability to train hard, easy fatigability, frequent infections, and depression.

Concerning exercising when sick, most clinical authorities in the area of exercise immunology recommend (Friman and Ilback, 1998; Mackinnon, 1999):

- If one has common cold symptoms (e.g., runny nose and sore throat without fever or general body aches and pains), intensive exercise training may be safely resumed a few days after the resolution of symptoms.
- Mild-to-moderate exercise (e.g., walking) when sick with the common cold does not appear to be harmful. In two studies using nasal sprays of a rhinovirus leading to common cold symptoms, subjects were able to engage in exercise during the course of the illness without any negative effects on severity of symptoms or performance capability (Weidner et al., 1997, 1998).
- With symptoms of fever, extreme tiredness, muscle aches, and swollen lymph glands, 2-4 weeks should

probably be allowed before resumption of intensive training.

## Vigorous Activity and Immune Function

A common perception among elite endurance athletes and coaches is that overtraining lowers resistance to URTI such as the common cold and sore throats. Many elite athletes have reported significant bouts with URTI that have interfered with their ability to compete and train. During the Winter and Summer Olympic Games, it has been regularly reported by clinicians that URTI are the most frequent and irksome health problems athletes experience (Nieman, 2000b).

The results of epidemiological studies generally support the belief that URTI risk is elevated during periods of heavy training and in the 1-2 week period following participation in competitive endurance races (Nieman et al., 1990a). A high percentage of self-reported illnesses occur when elite athletes exceed individually identifiable training thresholds, mostly related to the strain of training (Foster, 1998).

Although more athletes report URTI after a competitive race, it is still a small percentage. For example, only one in seven marathon runners reported an episode of URTI during the week following the March 1987, Los Angeles Marathon, compared to two in 100 who did not compete (Nieman et al., 1990a). URTI rates in marathon runners are even lower during the summer than winter/spring.

When athletes train hard, but avoid overreaching and overtraining, URTI risk is typically unaltered. For example, during a 2.5 month period (winter/spring) in which elite female rowers trained 2-3 hours daily (rowing drills, resistance training), incidence of URTI did not vary significantly from that of nonathletic controls (Nieman et al., 2000b).

Together, these data indicate that there is a relationship between exercise workload and infection (Figure 2). Most endurance athletes should experience low-to-normal URTI risk during periods of regular training, with URTI risk rising during periods of overreaching/overtraining and competition.

Is immune function in athletes modified in parallel with infection risk? (Figure 2). Two lines of investigation have provided insights both supporting and challenging this assumption (Nieman, 2000a):

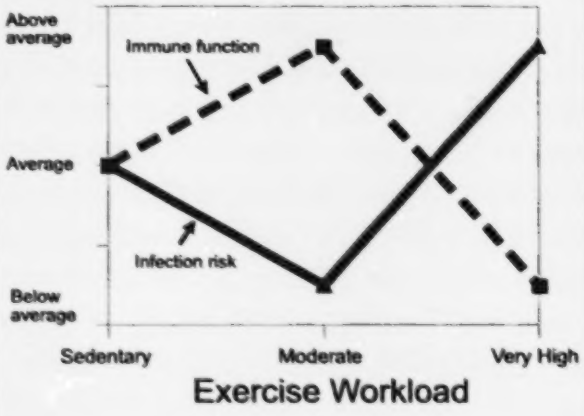


Figure 2.
Infection risk and immune function are related to the exercise workload.

- Does heavy exertion lead to temporary but clinically significant changes in immunity (i.e., the "open window" theory)?
- Do the immune systems of endurance athletes and nonathletes function differently when in a state of rest?

## Changes in Immunity Following Prolonged, Intensive Exercise

Immune function changes dramatically after each bout of prolonged and intensive exercise. During this "open window" of altered immunity (which may last between three and 72 hours, depending on the immune measure), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. Investigations are currently underway to demonstrate that individuals showing the most extreme immune suppression following heavy exertion are those that contract an infection during the following 1-2 weeks. This link must be established before the "open window" theory can be wholly accepted.

Several studies with animal models have provided important support of the "open window" theory. Davis et al. (1997), for example, have shown that in mice alveolar macrophage antiviral resistance is suppressed 8 h following prolonged strenuous exercise to fatigue, an effect due in part to an increase in circulating adrenal catecholamines.

Many components of the immune system exhibit change after heavy exertion, including the following (for review, see Nieman, 2000a; Mackinnon, 1999):

- Neutrophilia (high blood neutrophil counts) and lymphopenia (low blood lymphocyte counts), induced by high plasma levels of stress hormones such as epinephrine and cortisol.
- Decrease in NK cell cytotoxic activity (an important anti-viral measure), and mitogen-induced lymphocyte proliferation (a measure of T cell function).
- Decrease in the delayed-type hypersensitivity response (DTH). DTH is a complex immunological process that involves several different cell types (including T lymphocytes) and chemical mediators, and is manifested by firm, red skin indurations.
- Increase in plasma concentrations of pro- and anti-inflammatory cytokines (e.g., interleukin-6, interleukin-10, and interleukin-1 receptor antagonist). Cytokines are low molecular-weight proteins and peptides that help control and mediate interactions among cells involved in immune responses. Prolonged and intensive exercise bouts induce muscle cell injury, causing a sequential release of pro- and anti-inflammatory cytokines
- Decrease in nasal and salivary IgA concentration, nasal mucociliary clearance, and nasal neutrophil function. This indicates an impaired ability of the upper respiratory tract to clear external pathogens.
- Blunted major histocompatibility complex (MHC) II expression and antigen presentation in macrophages. The MHC antigens are essential for reactions of immune recognition. After phagocytosis and antigen processing, small antigenic peptides are bound to MHC II and presented to T-lymphocytes, an important step in adaptive immunity. These data imply that heavy exertion can blunt macrophage expression of MHC II, negatively affecting the process of antigen presentation to T-lymphocytes, and thus their ability to respond to a challenge by viruses.

These data suggest that immune function in several body compartments exhibits signs of stress or suppression for a short period following prolonged endurance exercise. Thus it makes sense that URTI risk may be increased when an athlete goes through repeated cycles of unusually heavy exertion, has been exposed to novel pathogens, and experienced other stressors to the immune system including lack of sleep, severe mental stress, malnutrition, or weight loss. A one-year retrospective study of 852 German athletes showed that risk of URTI was highest in endurance athletes who also reported significant stress and sleep deprivation (Konig et al., 2000). In other words, URTI risk is related to many factors, and when brought together, the athlete may be unusually susceptible.

## Resting Immune Function in Athletes and Nonathletes

Attempts thus far to compare resting immune function in athletes and nonathletes have failed to provide evidence that athletic endeavor is linked to clinically important changes in immunity, despite compelling epidemiological data (Nieman et al., 1993, 1995, 2000b; Tvede et al., 1991). Of all immune measures, only NK cell activity has emerged as a somewhat consistent indicator differentiating the immune systems of athletes and nonathletes. NK cells are highly active cells that combat certain types of viruses and cancer cells. In a study comparing elite female rowers and controls, NK cell activity measured 1.6-fold higher in the rowers (Nieman et al., 2000b). Elevated NK cell activity has also been reported in runners and cyclists (Nieman et al., 1995; Tvede et al., 1991). This increase in NK cell activity during most hours of the day should help the athlete clear viruses from the body, countering the stressful changes that occur in the immune system during the several hours after each bout of intensive exercise.

Neutrophils are important components of the innate immune system, aiding in the phagocytosis of many bacterial and viral pathogens, and the release of immunomodulatory cytokines. Neutrophils are considered to be the body's most effective phagocyte, and are critical in the early control of invading infectious agents. Neutrophil function has been reported to be suppressed in athletes, but this has not been a consistent finding, and may depend on the severity of training (Mackinnon, 1999).

Attempts thus far to link variances in both neutrophil function and NK cell activity with risk of infection have failed. Salivary IgA concentration warrants further research as a practical and inexpensive marker of potential infection risk in athletes. The secretory

immune system of the mucosal tissues of the upper respiratory tract is considered the first barrier to colonization by pathogens, with IgA the major effector of host defense (Mackinnon, 1999). In a study by Gleeson et al. (1999), salivary IgA levels measured in swimmers before individual training sessions showed significant correlations with infection rates, and the number of infections observed in the swimmers was predicted by the preseason and the mean pretraining salivary IgA levels. With runners, sickness rates following a competitive marathon race have been observed to be highest in those exhibiting the lowest salivary IgA levels (Nieman et al., 2001). In two other studies, however, variance in salivary IgA concentration was not related to a history of URTI incidence in elite female rowers or adolescent tennis athletes (Henson et al., 2000; Nehlsen-Cannarella et al., 2000). Thus the data are inconclusive, and research is needed with larger groups of athletes followed for longer periods of time to determine the usefulness of salivary IgA concentration in predicting URTI risk in athletes.

## Guidelines to Reduce the Risk of Infection

Nutrition impacts the development of the immune system, both in the growing fetus and in the early months of life. Nutrients are also necessary for the immune response to pathogens so that cells can divide and produce antibodies and cytokines. Many enzymes in immune cells require the presence of micronutrients, and critical roles have been defined for zinc, iron, copper, selenium, vitamins A, $B_6$, C, and E in the maintenance of optimum immune function (Nieman and Pedersen, 2000). The earliest research on nutrition and immune function focused on malnutrition. It has long been known that malnourished children have a high risk of severe and life-threatening infections. Protein-energy malnutrition adversely affects virtually all components of the immune system.

Should fitness enthusiasts use nutrient and herbal supplements to enhance immune function above and beyond the effects of physical activity? Despite all of the hype about supplements such as phytochemicals, antioxidants, flavonoids, carotenoids, glutamine (an amino acid), ginseng, and echinecea, there is insufficient evidence to warrant taking high doses in the belief they will prevent or cure ailments ranging from the common cold to cancer. In fact, extremely large doses may lead to health problems rather than confer benefits. The best practice is to eat a varied and balanced diet in accordance with energy needs and the U.S. Food Guide Pyramid, and be assured that vitamin, mineral, and phytochemical intake is adequate for both health and immune function (Nieman and Pedersen, 2000).

Whether one gets sick with a cold after a sufficient amount of the virus has entered the body depends on many factors that affect the immune system other than just physical activity and nutrition. Old age, cigarette smoking, mental stress, and lack of sleep have all been associated with impaired immune function, and an increased risk of infection (Mackinnon, 1999; Nieman, 2000b).

Based on current knowledge, good immune function can be maintained by regular physical activity, eating a well-balanced diet, keeping life stresses to a minimum, avoiding chronic fatigue, and obtaining adequate sleep. Immune function is suppressed during periods of very low caloric intake and quick weight reduction, so weight loss should be gradual to maintain good immunity.

For athletes, the influence of a growing list of nutritional supplements on the immune and infection response to intense and prolonged exercise has been assessed (Nieman and Pedersen, 2000). Supplements studied thus far include zinc, dietary fat, plant sterols, antioxidants (e.g., vitamins C and E, β-carotene, N-acetylcysteine, and butylated hydroxyanisole), glutamine, and carbohydrate. Of these, only carbohydrate has emerged as a useful nutritional countermeasure.

Several studies with runners and cyclists have shown that carbohydrate beverage ingestion plays a role in attenuating changes in immunity when the athlete experiences physiologic stress and depletion of carbohydrate stores in response to high intensity (~75-80% $VO_{2max}$) exercise bouts lasting longer than two hours (Gleeson et al., 1998; Nieman et al., 1997a, 1998a, 1998b). In particular, carbohydrate ingestion (about one liter per hour of a typical sports drink) compared to a placebo has been linked to significantly lower blood cortisol and epinephrine levels, a reduced change in blood immune cell counts,

and lower pro- and anti-inflammatory cytokines. These data suggest that the endurance athlete ingesting carbohydrate during the race event should experience a much lower perturbation in hormonal and immune measures compared to the athlete largely avoiding carbohydrate.

## Conclusions and Recommendations

By far, the most important finding that has emerged from exercise immunology studies is that positive immune changes take place during each bout of moderate physical activity. Over time, this translates to fewer days of sickness with the common cold and other upper respiratory tract infections. This is consistent with public health guidelines urging individuals to engage in near-daily physical activity of 30 minutes or greater. Other factors that help maintain good immune function include eating a well-balanced diet, keeping life stresses to a minimum, avoiding chronic fatigue, obtaining adequate sleep, and avoiding rapid weight loss.

Should the fitness enthusiast exercise when sick? In general, if the symptoms are from the neck up (e.g., the common cold), moderate exercise is probably acceptable and some researchers would argue even beneficial, while bed rest and a gradual progression to normal training are recommended when the illness is systemic (e.g., the flu). If in doubt as to the type of infectious illness, individuals should consult a physician.

Many components of the immune system exhibit adverse change after prolonged, heavy exertion lasting longer than 90 minutes. These immune changes occur in several compartments of the immune system and body (e.g., the skin, upper respiratory tract mucosal tissue, lung, blood, and muscle). During this "open window" of impaired immunity (which may last between three and 72 hours, depending on the immune measure), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. Thus risk of upper respiratory tract infections can increase when athletes push beyond normal limits.

# Physical Activity and Fitness Quote

**"Research has shown that during moderate exercise, several positive changes occur in the immune system. Although the immune system returns to pre-exercise levels very quickly after the exercise session is over, each session represents a boost that appears to reduce the risk of infection over the long term."**

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